REMARKS

The Examiner's Final Office Action dated December 5, 2001 has been carefully reviewed. In view of the above amendments made to the claims and for the reasons provided below, early allowance of pending claims 1 to 7 and 12 to 25 is respectfully requested.

I. 102 Rejections

The Examiner has rejected claims 1 to 5, 7, 10 to 18 and 21 under 35 U.S.C. 102(b) as being anticipated by Maniar et al. (WO 92/14449) and claims 1 to 6, 8 to 12, 15 and 20 under 35 U.S.C. 102(e) as being anticipated by Poli et al. (US 5,759,566).

In this connection, the Examiner's kind attention is invited to the fact that claim 1 has been amended to further specifically limit the constituent and structure of the solid lipophilic microparticle, thereby excluding the lipophilic microparticle disclosed in the prior art references cited by the Examiner. And the above 102 rejections are respectfully traversed for the reasons provided below.

1. Rejection of Claims 1 to 5, 7, 10 to 18 and 21under 35 U.S.C. §102(b)

i) Critical feature of the present invention

By way of review, the present invention, as defined in the amended claims 1 to 7 and 12 to 25, is directed to a solid lipophilic microparticle comprising a lipophilic substance, a water-soluble excipient and an active ingredient selected from the group consisting of a protein drug, a peptide drug and an antigen, and a sustained-release formulation thereof for an effective *in vivo* delivery of the drug or antigen.

The solid lipophilic microparticle of the present invention is prepared by coating the active

ingredient with the water-soluble excipient at first to form the solid microparticle, and then, coating the surface of the solid microparticle with the lipophilic substance.

ii) Summary of the Maniar patent

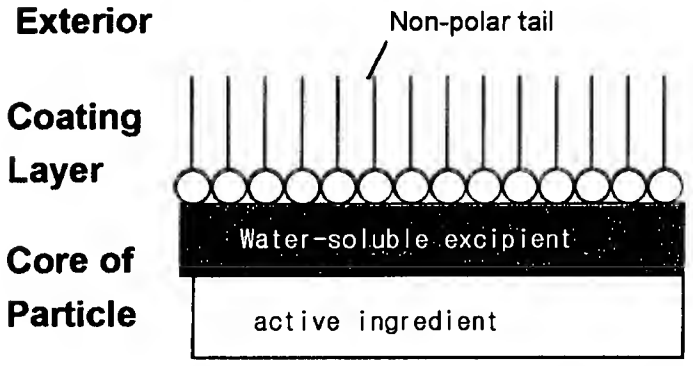
The Maniar patent discloses a controlled delivery protein microparticle comprising a biologically active protein or peptide incorporated into a microparticle formed of fatty acid or fatty acid anhydride monomers or dimers. The microparticle disclosed in the Maniar patent is prepared by the steps of: providing a dry protein powder; mixing the protein with melted fatty acid or fatty acid anhydride at a temperature below the protein denaturation temperature; and then solidifying the melted mixture.

iii) Comparison of the present invention with the Maniar patent

Simply stated, the Maniar patent is totally silent on the inner coating of a water-soluble excipient as claimed in the amended claim 1 of the present invention. It is submitted that the lipophilic microparticle disclosed in the Maniar patent has a different structure from the solid lipophilic microparticle of the present invention, which results in the difference in stability, sustained-release characterictics, injectibility and dispersability of the microparticle for a drug delivery.

As illustrated in Figure 1 produced below, the solid lipophilic microparticle of the present invention has a dual-coated structure. First, a protein drug, a peptide drug or an antigen is coated with a water-soluble excipient such as hyaluronic acid to form a solid microparticle. Thanks to this primary coating of a water-soluble excipient, the active ingredient is not denatured, retaining its full activity, and the solid microparticle attains an improved sustained-release effect. The solid microparticle having such primary coating of a water-soluble excipient is then coated with a lipophilic substance, which is an amphipathic substance having polar (hydrophilic) head and aliphatic (hydrophobic) tail groups. The

hydrophilic polar groups bind to the surface of the solid microparticle coated with the water-soluble excipient, and the hydrophobic groups extend outward, which results in a solid lipophilic microparticle having a surface endowed with a lipophilicity. As a result, the solid lipophilic microparticle of the present invention is endowed with an improved dispersability in a lipophilic medium such as an oil, giving an improved *in vivo* absorption rate.



<Figure 1> Structure of the inventive solid lipophilic microparticle

In contrast, the Maniar patent merely discloses the dispersion of a biologically active protein in a lipophilic substance such as fatty acid or fatty acid anhydride. With the lipophilic subatance layer taught in the Maniar patent, it is not possible to guarantee the stability of the active ingredient which directly contacts with an organic solvent used for dissolving the lipophilic substance. It should be noted that the dual-coated structure in accordance with the present invention makes it possible to prevent the active ingredient from denaturing and give a sustained-release effect to the solid lipophilic microparticle.

Further, while the improved sustained-release effect of the solid lipophilic microparticle of the present invention results from the primary coating of an active ingredient with a water-soluble excipient, the controlled delivery effect of the microparticle of the Maniar patent apparently stems from dispersing the biologically active protein in a fatty acid or fatty acid anhydride used as a carrier.

Accordingly, the Maniar patent clearly fails to teach the doubly coated solid lipophilic

microparticle of the present invention in terms of both constituent and structure; and, accordingly, it is respectfully submitted that the present invention is both novel and inventive over WO 92/14449.

2. Rejection of Claims 1 to 6, 8 to 12 and 20 under 35 U.S.C. §102(e)

i) Summary of the Poli patent

The Poli patent discloses that a liquid pharmaceutical composition of a protein or peptide drug comprising (a) a microemulsion containing the drug, said microemulsion consisting of a hydrophilic phase, a lipophilic phase and surfactants, and (b) a copolymer thickener.

ii) Comparison of the present invention with the Poli patent

Poli et al. discloses a lipophilic microparticle comprising a protein or peptide drug and a lipophilic substance such as hyaluronic acid (Example 3) or lecithin (Example 4), but not the doubly coated solid lipophilic microparticle of the present invention. Namely, the Poli patent merely discloses the lipophilic microparticle prepared by incorporating a copolymer thickener into a liposomic dispersion or microemulsion formed using a proteinaceous substance coated only with a lipophilic substance.

Specifically, the hyaluronic acid in Example 3 is used simply as an absorption promoter for the purpose of enhancing a drug absorption rate. In contrast to the Poli patent, the hyaluronic acid of the present invention is used to coat the active ingredient as a water-soluble excipient, thereby improving the stability and sustained-release effect. Therefore, it is submitted that the hyaluronic acid disclosed in the Poli patent has a different purpose and function from that of the present invention.

In case of Example 4, a microemulsion is formed by mixing a lipophilic phase obtained by

dissolving lecithin in a mixture of isopropyl myristate and ethyl alcohol with calcitonin. As mentioned previously, this Example uses an organic solvent that tends to denature the protein drug, due to the action of dissolving biodegradable lecithin to form the lipophilic phase. In order to prevent such problem, the present invention offers a solid lipophilic microparticle which is successively coated with a water-soluble excipient and a lipophilic substance, thereby having a dual-coated structure.

It is, therefore, clear that the Poli patent does not teach or suggest the doubly coated solid lipophilic microparticle of the present invention. Accordingly, and it is respectfully submitted that the present invention is both novel and inventive over US 5,759,566.

II. 103 Rejections

The Examiner has rejected claim 19 under U.S.C. 103(a) as being unpatentable over Poli et al.; and claim 22 under U.S.C. 103(a) as being unpatentable over Poli et al. or Maniar et al. as applied to claims 1 to 21 above, and further in view of Chen et al.'s article published in Journal of Virology 72 (1997), pp. 5757-5761.

i) As to rejection of claim 19

Claim 19, in addition to the inventive features recited in claim 1, defines an oil-in-water emulsion formulation of the inventive solid lipophilic microparticle, which provides an improved vaccine formulation. The emulsion formulation of claim 19 is comprised of an oil phase containing solid lipophilic microparticles of a first antigen and an aqueous phase containing a second antigen.

On the other hand, the Poli patent cited as the primary reference by the Examiner is merely directed to a lipophilic microparticle containing a protein drug coated with a lipophilic substance only which does not have a dual-coated structure of the solid lipophilic

microparticle as in the amended claim 1 of the present invention.

Further, the inventive feature of claim 19 is not to just load a plurality of antigens into a microparticle system, but to preserve multiple antigens separately in the aqueous and the oil phases, thereby preventing undesirable interactions between the antigens. If a mixed vaccine formulation were prepared by simply incorporating two incompatible antigens into a microparticle as in the Poli patent, this formulation would undoubtedly be devoid of the advantages of the inventive formulation.

Accordingly, it is respectfully submitted that claim 19 defines a patentable and unobvious invention over the Poli patent.

ii) As to rejection of claim 22

It is also believed that claim 22 is allowable for the same reasons indicated with respect to the amended claim 1, and further because the additional features recited therein further distinguished the present invention from the cited references.

Claim 22 specifically defines that the antigen used in the solid lipophilic microparticle as the active ingredient is an attenuated, killed or recombinant antigen.

The Examiner pointed out that the incorporation of DNA as an antigen into the microparticles of Poli et al. or Maniar et al. may be motivated by one of ordinary skilled in the art in view of the Chen reference which discloses a rotavirus VP6 DNA vaccine encapsulated in poly(lactide-coglycolide) (PLG) microparticle that may result in protective immunity against subsequent ratovirus challenge.

However, as mentioned previously, the Maniar and Poli patents are entirely silent on the doubly coated solid lipophilic microparticle of the present invention. In addition, the

microparticles containing the DNA vaccine as disclosed in the Chen reference are prepared by simply emulsifying the plasmid encoding rotavirus VP6 DNA with PLG, and, accordingly, it is far from being relevant to the present solid lipophilic microparticle.

As a matter of established principle, the Examiner's hindsight combination of Chen and any one of Poli or Maniar is believed to be improper in the absence of any suggestion, teaching or motivation given in any of the prior art references to do so, and inasmuch as one skilled in the art whould have no reason to make such combination.

Furthermore, even assuming, *arguendo*, that such combination were proper, such combination still cannot render the present invention obvious because none of Chen, Poli, and Maniar teaches or implies the present invention. Accordingly, even if every single disclosure contained in each of the references is selectively chosen and stacked together against the present invention, such combination cannot possibly suggest to an ordinary person skilled in the art the inventive features of the present invention.

III. Conclusion

In view of the foregoing amendments and discussions, it is respectfully submitted that the present invention as defined in the pending claims 1 to 7 and 12 to 25 is in full compliance with all the statutory requirements, and, therefore, it is earnestly requested that the Examiner's rejections be withdrawn and the pending claims be allowed in their present form.

Respectfully submitted,

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Version with markings to show changes made

A "marked up" version of claim 1 follows:

1. (Twice Amended/Marked up) A solid lipophilic microparticle comprising a lipophilic substance, a water-soluble excipient and an active ingredient selected from the group consisting of a protein or peptide drug and an antigen, wherein [the surface of the microparticle is coated with the lipophilic substance] the active ingredient is coated with the water-soluble excipient at first to form a solid microparticle, and, then, the surface of the solid microparticle is coated with the lipophilic substance.